ORIGINAL RESEARCH ARTICLE

Drug Safety 2001; 24 (9): 703-713
0114-5916/01/0009-0703/$22.00/0

Safety Profile of Tolterodine as Used in General Practice in England

Results of Prescription-Event Monitoring

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Abstract

Background: Unstable bladder symptoms are a common problem in general practice. Drug therapy with anticholinergic drugs is frequently used in the management of this condition. However such drugs are associated with a high incidence of anticholinergic adverse effects. Tolterodine is a competitive anticholinergic agent, selective for the bladder as opposed to the salivary glands.

Objective: To monitor the safety of tolterodine as used in general practice patients in England for the treatment of urinary frequency, urgency and incontinence.

Design: Prospective observational cohort study.

Patients and participants: 14 526 patients [mean age 62.7 (SD 16.4) years; 68.6% female].

Methods: Patients prescribed tolterodine in general practice, soon after the release of the drug in the UK, were followed up for a minimum of 6 months using the technique of prescription-event monitoring (PEM).

Results: The most common adverse events reported were dry mouth, headache, malaise, constipation, dyspepsia, nausea and vomiting and pain in abdomen. We identified some uncommon events as possible adverse drug reactions – notably hallucinations, tachycardia and palpitations. The prevalence of these events was compared with that in patient cohorts for other drugs on the PEM database. The age- and sex-adjusted relative risk of hallucinations on tolterodine compared with 10 drugs of other therapeutic classes, and with terodiline, another drug indicated for bladder instability, was 4.85 [95% confidence interval (CI) 2.72 to 8.66] and 1.25 (95% CI 0.62 to 2.53), respectively. There was no significant difference for tachycardia/palpitation in this comparison.

Conclusions: Tolterodine is well tolerated in general practice at the recommended daily dose. Hallucinations, tachycardia and palpitations are infrequently associated with the drug.

Tolterodine is a specific competitive cholinergic receptor antagonist, which shows selectivity for the urinary bladder as opposed to the salivary glands. It is indicated for the treatment of unstable bladder symptoms. The parent compound, tolterodine L-tartrate is mainly metabolised by the enzyme cytochrome P450 (CYP) 2D6, resulting in the production of a pharmacologically active 5-hydroxymethyl metabolite.[1] This metabolite has some muscarinic adverse effects, e.g. dry mouth and eye problems, especially with accommodation, but these are reported to be less prominent than with oxybutynin.[2] Unstable bladder symptoms are a common problem in general practice, and tolterodine is commonly prescribed. This paper reports the results of an observational cohort study undertaken to examine the safety of tolterodine as used by general practitioners in England.

Methods

Prescription-event monitoring (PEM) is used as a form of postmarketing surveillance for newly licensed drugs introduced to the UK market. The methodology of PEM has been fully described in the literature.[3] Patients were identified from dispensed National Health Service (NHS) prescriptions for tolterodine, written by general practitioners (GPs) in England, in the immediate postmarketing period. Prescription data for the whole of England was supplied electronically, in confidence, by the Prescription Pricing Authority between April 1998 and December 1998.

Questionnaires (called 'green forms') were posted to the prescribing GPs between November 1998 and May 1999, approximately 6 months following the first prescription for the drug. No reminder forms were employed. These green forms requested information on the age, diagnosis, duration of treatment (start and stop dates) and other details, including any significant events that may have occurred in the patients' medical history since the day the drug was started. The term 'event' was defined as 'any new diagnosis, any reason for referral to a consultant or admission to hospital, any unexpected deterioration (or improvement) in a concurrent illness, any suspected drug reaction, any alteration of clinical importance in laboratory values, or complaint of sufficient importance to enter into the patient's notes'. We asked the doctor to record the reason for stopping the drug (if appropriate), and also to indicate any events that were considered to be an adverse drug reaction. The indication was taken to be constant while receiving treatment. Thus, in PEM the exposure data are derived from the original prescriptions for the drug being monitored and the outcome data are the events recorded by the original prescribers on the green forms.

All reported events were coded onto a computer by using a dictionary arranged in a system organ classification, with 'lower' terms grouped together under broader 'higher' terms.[4] In PEM, signals are generated by the report of a typically iatrogenic reaction; by an event having an unusually high incidence density (ID) or event ranking; or by a temporal pattern emerging over time. Possible signals and all reported pregnancies were followed up by writing to the patient's general practitioner, or hospital consultant, for further information. Deaths with no specified cause were followed up by obtaining death certificates from the Office for National Statistics (ONS). If a death was considered to be 'possibly' related to tolterodine, the general practice records were requested from the Local Health Authority, after first gaining permission from the general practitioner; postmortem results were reported when appropriate.

Possible signals during treatment with tolterodine were compared with selected comparator drugs. The first comparator cohort included 10 drugs of different therapeutic class held within the PEM database. These drugs have indications other than for bladder instability. The second included terodiline, a drug indicated for bladder instability, but with mixed pharmacological properties. A list of the individual drugs, study dates and response rates is provided in table I.

Statistical Analysis

IDs were calculated for all reported events dur-

Table I. Collection periods and response rates for comparator drugs

Drug	Study dates	Response rate (%)	Cohort size[a]
Acarbose	July 1993 to August 1995	57.1	13 655
Alendronate	October 1995 to January 1997	53.8	11 916
Famotidine	November 1987 to March 1988	46.6	9 500
Finasteride	October 1992 to February 1994	57.8	14 772
Lanzoprazole	May 1994 to November 1994	47.2	17 329
Meloxicam	December 1996 to March 1997	49.7	10 444
Misoprostol	October 1988 to July 1989	65.5	13 775
Nizatidine	September 1987 to September 1988	40.0	7 782
Omeprazole	June 1989 to June 1990	56.9	16 204
Pantoprazole	December 1996 to June 1997	41.0	11 541
Terodiline	November 1986 to September 1997	62.0	12 444

a Relates to whole study period.

ing treatment within any specified time period. The figures were expressed as the number of the first reports of an event per 1000 patient-months of treatment. IDs for events occurring in the first month of treatment (ID_1), during months 2 to 6 of treatment (ID_2) and for events occurring during the overall treatment period (ID_a) were calculated in patients for whom either the date of stopping the drug is known, or in those who continued to take the drug. The difference between the 2 rates (ID_1 minus ID_2) was calculated to test the hypothesis that the rate did not change over time. Where the arithmetic difference between ID_1 and ID_2 was significantly above 0 at the level of $p = 0.01$, this was considered to be a signal of a possible adverse drug reaction.

Crude rate ratios (RR) for possible signals were calculated for the first 6 months of treatment using Mantel-Haenszel methods. For each drug only those events of interest reported within the first 6 months on treatment were included. Any events reported without an event date specified were excluded. Events occurring after 30 days from the start date, and where no stopping date was given, were also excluded, as were events occurring more than 30 days after stopping the drug. Missing values were accounted for in the analysis by the exclusion of participants with missing values for each individual variable under investigation. Age and sex have been shown to affect the reporting of adverse drug reactions and the rates of prescribing of drugs of different therapeutic classes.[5] The data were stratified by age and sex, and an adjusted RR calculated. Evidence of confounding was assessed by comparing crude with adjusted RR, and association with drug group. Evidence for effect modification was investigated by examining stratum-specific RR and homogeneity test results. In additon to the time to onset of selected events, the cumulative survival of each cohort was calculated with the Kaplan-Meier method and compared using the log-rank test.

Data for each drug were extracted from the IBM AS400 mainframe computer at the Drug Safety Research Unit (DSRU), and from files arranged by individual patient for each event reported. This was carried out partly in an Excel spreadsheet and partly in an Access database. Data manipulation was performed in Excel, Access and STATA.

Sample Size

The ability to detect an adverse drug reaction (ADR) is dependent upon the expected incidence rate of that ADR for those exposed, the background rate in those unexposed and the number of patients available. A sample size of 10 000 patients should allow for the detection of at least 3 cases of an ADR if it occurs with an annual incident rate of between 1 in 1000 and 1 in 2000 patients, assuming that it is very rare as a background event, with power, $1-\beta$, given as 0.80.[6]

Table II. Incidence densities (ID) for events with possible causal association with tolterodine, in order of number of events in month 1

Event	No. of events		Rate per 1000 patient-months of treatment				No. of events during total follow-up period	No. of ADRs	Incicence rise (%)[a]
	month 1	months 2-6	month 1 (ID_1)	months 2-6 (ID_2)	total (ID_a)	ID_1–ID_2 (99% CI)			
Dry mouth	210	176	16.5	4.3	5.7	12.1 (9.1-15.2)	423	80	2.9
Headache, migraine	118	107	9.2	2.6	3.5	6.6 (4.3-8.9)	260	29	1.8
Unspecified adverse effects	96	68	7.5	1.7	2.4	5.8 (3.8-7.9)	179	179	1.2
Urinary tract infection	96	204	7.5	5.0	5.4	2.5 (0.3-4.7)	397	1	2.7
Micturition disorder	95	139	7.4	3.4	4.0	4.0 (1.9-6.1)	293	1	2.1
Malaise, lassitude	90	99	7.1	2.4	3.0	4.6 (2.6-6.6)	222	19	1.5
Intolerance	86	53	6.7	1.3	2.1	5.4 (3.5-7.4)	152	14	1.0
Constipation	85	100	6.7	2.5	3.1	4.2 (2.2-6.2)	227	16	1.6
Dyspepsia	85	132	6.7	3.2	3.6	3.4 (1.4-5.4)	265	26	1.8
Dizziness	75	81	5.9	2.0	2.4	3.9 (2.0-5.7)	179	20	1.2
Nausea, vomiting	74	82	5.8	2.0	2.5	3.8 (1.9-5.6)	183	17	1.3
Pain abdomen	70	88	5.5	2.2	2.4	3.3 (1.5-5.1)	179	9	1.2
Diarrhoea	51	65	4.0	1.6	1.9	2.4 (0.9-3.9)	139	7	1.0
Depression	49	85	3.8	2.1	2.2	1.7 (0.2-3.3)	164	3	1.1
Drowsiness, sedation	43	26	3.4	0.6	1.0	2.7 (1.4-4.1)	73	15	0.5
Visual defect	37	39	2.9	1.0	1.2	1.9 (0.6-3.2)	86	14	0.6
Pain chest, tight chest	30	43	2.4	1.1	1.3	1.3 (0.1-2.5)	96	7	0.7
Retention	30	29	2.4	0.7	0.9	1.6 (0.5-2.8)	66	3	0.5
Insomnia	24	22	1.9	0.5	0.7	1.3 (0.3-2.4)	52	6	0.4

a Proportion of events reported for study cohort (n = 14 526).

ADR = adverse drug reaction (as reported by general practitioner); **CI** = confidence interval.

Confidentiality

The study was conducted in accordance with the International Ethical Guidelines for Biomedical Research, prepared by the Council for International Organisations of Medical Sciences.[7]

Results

We identified 35 295 patients who had commenced treatment during the specified time period. The anticipated sample size of 10 000 was exceeded sooner than expected with only 26 991 green forms having been sent out. A total of 14 526 forms were returned with useful information, giving a response rate of 53.8%. The mean age of the cohort was 62.7 years (SD 16.4 years) and 68.6% of the cohort were female.

The events reported most frequently are shown in table II, ranked in descending order according to the ID of events experienced in the first month. Table 2 shows the specific events (relating to symptoms or diagnoses) for which ID_1 to ID_2 was significantly greater than 0 at the $p = 0.01$ level. This value is important, for it may signal that the event is associated with the drug, based on the considerations of the typical time distribution of ADRs. Table II shows that dry mouth and headache were the 2 most common events likely to be linked to the drug.

The events identified by the general practitioner as suspected ADRs to tolterodine include those already mentioned in the summary of product characteristics.[1] Common events (>1 in 100 patients) as listed in the summary of product characteristics were, in descending order of ID_1 per 1000 patient months: dry mouth, headache/migraine, constipation, dyspepsia, nausea and vomiting, and pain in abdomen. Events regarded as less common (<1 in 100 patients) were: visual defect, and pain in chest. Events coded as 'micturition disorder' and 'retention' are symptoms characteristic of the underlying condition. The most common reasons for stopping

treatment were: dry mouth (250 patients), unspecified adverse effects (168 patients), headache (123 patients), constipation (78 patients) and general malaise (78 patients).

Selected Events

Examination of the listing of events during treatment and those resulting in discontinuation of treatment did reveal some that were considered to be of medical interest, although they did not occur in sufficient numbers to generate a signal of causal association with the drug, using the ID_1 to ID_2 statistic. These events were as follows: (i) hallucinations; (ii) tachycardia; (iii) other cardiac arrhythmias (including extrasystoles and atrial fibrillation); (iv) pain in chest; and (v) palpitations. Individual case reports were assessed for causality by a medically qualified clinical research fellow, using 4 basic considerations (temporality, pharmacological plausibility, clinical and pathological characteristics of the event, likelihood or exclusion of other possible causes) and 5 categories (probable, possible, unlikely, awaiting further information or unassessable). Details of causal assessment on these events are shown in table III. Further details of case history for selected patients experiencing these events were obtained, in confidence, by follow-up from the GP.

Psychiatric Events

In none of the cases judged to be 'probably' or 'possibly' causally related was the dosage above the recommended maximum (4mg per day). The predominant type of hallucination was visual. Most occurred in elderly patients, of whom 89% were female (compared to the proportion of 68% of females in the tolterodine study cohort in this age group; Fisher's exact $p = 0.29$). The dosage was either 2 or 4mg per day.

Cardiovascular Events

In most cases of tachycardia, or other arrhythmia, the exact nature of the rhythm was not specified, although in 1 case (a 76-year-old male) supraventricular tachycardia was diagnosed. Only 5 cases reported confirmation by electrocardiogram (ECG). There were no reported cases of serious cardiac arrhythmia such as ventricular tachycardia or fibrillation. These events occurred in either sex and in a wide age range (youngest patient aged 29 years). The dosage was 1, 2 or 4mg per day. In the cases of chest pain 'possibly' causally related to drug ingestion, there was a wide variation in symptomatology, which was sometimes linked with other anticholinergic effects such as dry mouth and nausea and also sometimes linked with abdominal pain. A specific pattern to the nature of the chest pain was not discernible, although it did occur predominantly at the dosage of 4mg per day [16 of 17 cases (94%) where dosage known]. Chest pain is listed as a possible ADR to tolterodine in the summary of product characteristics.[1]

Table III. Details of events selected for follow-up

Event	No. of events reported on treatment	No. of events judged to be probably or possibly related	Median dosage (mg/day)	Median age (interquartile range) [years]	Sex	
					male	female
Hallucinations	23	9[a]	4	79 (70 to 92)	1	8
Palpitations/tachycardia	42	17[b](13 palpitations and 4 tachycardia)	3	65 (51 to 71)	8	9
Other cardiac arrhythmias	29	4 (2 extrasystoles and 2 atrial fibrillation)	4	57.5 (53 to 74)	2	2
Chest pains	87	21[a]	4	67 (33 to 79)	6	12[c]

a 1 age unknown.
b 4 age unknown.
c 3 sex unknown.

Other Events of Interest

Other events of interest were as follows. One patient (a 65-year-old male) developed a cutaneous reaction diagnosed as erythema multiforme a few days after starting tolterodine on 4mg per day. This was ascribed by his general practitioner to ingestion of tolterodine, which was accordingly stopped and the rash cleared up. Another patient (an 87-year-old male) was known to have had Alzheimer's disease at the time of starting tolterodine. The prescribing doctor noted that his cognitive function declined as the dosage of tolterodine was increased and improved when he stopped the drug. There were 2 female patients (aged 43 and 65 years) who developed nightmares soon after starting tolterodine, both at 4mg per day. In both cases the drug was stopped and the nightmares disappeared.

Out of 1481 women of childbearing age (15 to 45 years), 20 pregnancies were reported, 3 of which were planned. For the unplanned, only 1 reported contraceptive use. The summary of product characteristics recommends that women of childbearing age should be considered for treatment only if using adequate contraception.[1] One woman stopped use in anticipation of planned pregnancy. Ten women stopped taking the drug as a result of pregnancy. In 6 pregnancies, tolterodine was taken during the first trimester at a median daily dosage of 4mg (range 1 to 4mg). Of these, 5 resulted in live births with no congenital abnormalities, and 1 in spontaneous abortion. There were no records of tolterodine use later in pregnancy.

Table IV. Characteristics of study cohort

Characteristic	Tolterodine	Comparator cohort[a]	Terodiline[b]
Study cohort			
Number	14 526	135 492	12 423
Mean age (SD) [years]	62.7 (16.4)	60.1 (15.8)	63.7 (17.5)
Males			
number (%)	4540 (31.4)	64 013 (47.2)	3376 (27.2)
mean age (SD) [years]	65.8 (15.4)	58.6 (15.8)	65.5 (16.1)
Females			
number (%)	9923 (68.6)	69 918 (51.6)	8912 (71.6)
mean age (SD) [years]	61.4 (16.7)	61.5 (15.6)	63.1 (18.0)
Sex not known [number (%)]	64 (0.4)	1561 (1.2)	135 (1.1)
Age not known [number (%)]	2329 (16.0)	14 977 (11.1)	2018 (16.2)
Hallucinations			
Number	22	34	14
Males [number (%)]	7 (31.8)	14 (41.2)	14 (100)
Females [number (%)]	15 (68.2)	20 (58.8)	0 (0)
Mean age (SD) [years]	75.4 (13.1)	71.1 (14.7)	81.2 (7.1)
Sex not known	0	0	0
Age not known	3	2	0
Palpitations/tachycardia			
Number	40	306	24
Males [number (%)]	12 (30)	110 (35.9)	4 (16.6)
Females [number (%)]	28 (70)	195 (63.7)	19 (79.2)
Mean age (SD) [years]	63.0 (14.9)	62.9 (13)	56.9 (17.5)
Sex not known	0	1	1
Age not known	4	10	0

a 70 patients excluded.
b 21 patients excluded.

There were 379 deaths reported during the follow-up period. For 20 of these, we have been unable to ascertain the cause of death after extensive attempts to obtain the death certificates. The underlying cause of death was of cardiovascular origin for 140 cases, cancer for 101 cases and noncardiovascular origin for 118 cases. For those deaths of cardiovascular causes, 3 occurred within the first month, 1 of which was associated with disorders of cardiac rhythm. None of the deaths were thought attributable to use of tolterodine after causality assessment by a medical practitioner. Data for age, sex and duration of treatment were incomplete, preventing an estimation of the expected number of deaths in this population.

Univariate Analysis

We compared the crude prevalence of 2 possible signals, hallucinations and palpitations/tachycardia combined, for tolterodine with both comparator cohorts. Characteristics of study cohorts are presented in table IV.

Age was split into quartiles according to distribution of the overall cohort. Cross-tabulation of potential confounders (age and sex) with the events and drug cohort suggested significant association between age and hallucinations ($p < 0.001$), cardiac events ($p = 0.021$) and drug cohort ($p < 0.001$). The old elderly (>74 years) had the highest risk of experiencing a psychiatric event, and being prescribed medication. People 50 years and under had the lowest risk of experiencing a cardiac event of interest. Similarly, sex was significantly associated with hallucinations ($p = 0.013$), cardiac events ($p < 0.001$) and drug cohort ($p < 0.001$); women were more likely to experience an event and be prescribed medication.

Table V shows crude event rates per 1000 person-years by drug cohort. Members of the cohort were followed up for a total of 51 988 person-years, and during this time hallucinations were reported in 70 patients and 370 palpitation/tachycardia events were reported in 360 patients. For purposes of this study the first event was recorded.

Table V. Rate (per 1000 patient-years) of selected events for drug cohorts

Exposure cohort	Hallucination rate (95% CI)	Palpitation/tachycardia rate (95% CI)
Tolterodine	4.46 (2.94-6.78)	8.11 (5.95-11.06)
Comparator	0.79 (0.57-1.11)	7.12 (6.37-7.97)
Terodiline	3.42 (2.03-5.78)	5.86 (3.93-8.75)

CI = confidence interval.

The unadjusted rate of hallucinations does appear to differ between the exposed (tolterodine) and the comparator cohorts. Table VI presents crude and adjusted Mantel-Haenszel RR between the cohorts. The crude unadjusted RR suggested that patients taking tolterodine are over 5 times more likely to experience hallucinations than are patients taking the comparator drugs, and terodiline users are over 4 times more likely to experience hallucinations than the comparator cohort. Controlling for identified risk factors reduced the size of the effect: after adjustment for age and sex there was still a strong association between tolterodine use and hallucination event (RR 4.85), and after adjustment for age between terodiline and hallucinations (RR 4.03). The crude unadjusted RR for palpitation/tachycardia events suggested a weak difference between the cohorts. Adjustment for age and sex had nonsignificant effects on RR estimate, with evidence of effect modification by age.

The cumulative survival of each cohort was calculated to obtain an estimate of the survival experience of patients separately for hallucinations and palpitation/tachycardia events (figs 1 and 2). The median survival estimate in days is given for each group respectively. The log-rank test was performed to test the hypothesis that there was no difference in survivorship between groups. The result for hallucinations shows that the 3 groups had significantly different cumulative survivals ($p < 0.0001$), with those exposed to tolterodine experiencing over 3 times the expected number of events (22 instead of 6.7), and terodiline experiencing twice the number expected (14 instead of 5.6). Conversely the log-rank test for palpitation/tachycardia events showed that the 3 groups had similar cumulative survivals ($p = 0.4335$).

Table VI. Relative risk of hallucinations and cardiac events (combined) between drug cohorts

Event	Rate ratio	95% CI for rate ratio	p-Value
Tolterodine *vs* comparator			
Hallucinations			
Crude	5.63	3.30-9.64	<0.0001
MH estimate adjusted for age and sex	4.85	2.72-8.66	<0.0001
Palpitations/tachycardia			
Crude	1.14	0.82-1.58	0.4397
MH estimate adjusted for age and sex	1.05	0.74-1.49	0.7762
Tolterodine *vs* terodiline			
Hallucinations			
Crude	1.30	0.67-2.55	0.4370
MH estimate adjusted for age[a]	1.25	0.62-2.53	0.5287
Palpitations/tachycardia			
Crude	1.38	0.83-2.29	0.2078
MH estimate adjusted for age and sex	1.30	0.77-2.20	0.3245
Terodiline *vs* comparator			
Hallucinations			
Crude	4.32	2.32-8.06	<0.0001
MH estimate adjusted for age[a]	4.03	2.09-7.75	<0.0001
Palpitations/tachycardia			
Crude	0.83	0.54-1.25	0.3593
Adjusted for:			
age[b]	0.94	0.61-1.43	0.7610
sex	0.71	0.46-1.08	0.1121

a Sex not adjusted for as no females experienced event.

b Test for heterogeneity p value = 0.482.

CI = confidence interval; **MH** = Mantel-Haenszel method.

Discussion

The bladder selectivity of tolterodine has been reported to improve tolerability compared with other muscarinic receptor antagonists,[8,9] This study generally supports this view. Most adverse events were predictable anticholinergic effects (e.g. dry mouth, gastrointestinal upset and visual problem) which occurred comparatively infrequently (<20 per 1000 patient-months in the first month of treatment). There were, however, some events which occurred rarely ($ID_1 \leq 1$ per 1000 patient-months), but which appear, after careful follow-up, to be causally linked to the drug. These events were hallucinations, palpitations and tachycardia. These are symptoms related to severe central acetylcholinergic receptor antagonism, and are mentioned as such in the summary of product characteristics for tolterodine.[1] However, none of the cases we report here were related to overdose.

Data for evidence of dose-event relationship are sparse. A comparison of incidence rates for equivalently effective doses would be preferable, but data for dose at event although requested are not always provided on the green form questionnaires, and so the incidence rate reflects the entire starting dose range used. Furthermore, PEM data exclude information on other potential confounders. GPs are not asked to routinely report concomitant medication. Drugs that affect the hepatic CYP system may affect drug plasma concentrations such that toxic concentrations are attained, increasing risk of adverse events; the summary of product characteristics recommends care with coprescribing of drugs metabolised primarily through the liver and dosage reduction in patients with impaired liver function.[1] Although data on concomitant medication are provided upon follow-up, likely interactions with tolterodine were excluded in those patients in whom causality was assessed as 'probable or possible'.

Ideally one would wish to compare tolterodine with a drug of similar therapeutic class and indication. Comparison with terodiline is questionable in that it is a drug with mixed pharmacological properties with both antimuscarinic and calcium antagonist properties, so the comparison would not be pure. Terodiline was withdrawn worldwide on suspicion of cardiac toxicity,[10] and data for no other anticholinergic drug are held on the DSRU database. The second comparator cohort was obtained from pooled data from the database for drugs whose pharmacological action were not related to antimuscarinic activity, cardiovascular or CNS activity. Hence, the number of studies for which data are held on the DSRU PEM database restricts choice. In this study, data from the comparator drugs were collected over different calendar periods which

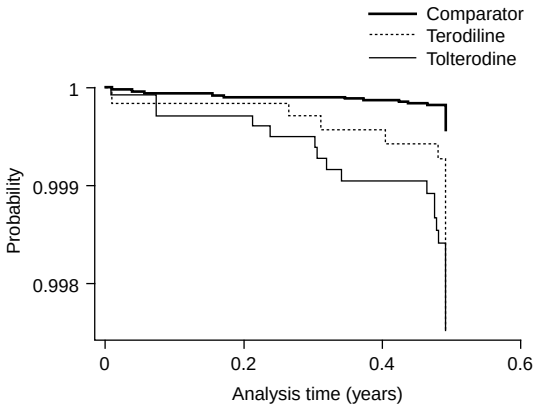

Fig. 1. Kaplan-Meier probability of remaining free of hallucinations, by drug cohort. Median time (interquartile range) [days] to event: comparator 76 (21 to 132), tolterodine 62.5 (20 to 125), terodiline 81 (33 to 150) [p < 0.0001, log-rank test].

may have affected the comparability between the cohorts. An important source of bias is that the studies were completed over a number of years (between 1989 and 1999). However, comparative PEM studies between the first and latest drug in other therapeutic groups has demonstrated that incidence of events is reasonably constant, arguing against differential reporting.[11] Regarding data collection, not all returned forms contain clinically useful data, which could conceal selection bias.

The arithmetic difference between the 2 rates, ID_1 and ID_2, is calculated in order to test the null hypothesis that the rate for the event does not change over time. This figure may be important for it may signal that an event is associated with the drug, especially for predictable (Type A) reactions which may occur shortly after taking the drug. For hallucinations and palpitation/tachycardia events, there is only weak evidence of a signal using this method. Analysis of cumulative survival probability to the selected events indicates that the events occur in the second month for all groups. This indicates that for delayed events the former method may not be sensitive enough, especially where the numbers are relatively small.

We can find no reports in the literature of hallucinations as an ADR to tolterodine. The Medicines Control Agency (MCA) in the UK had received eight reports of hallucinations up until September 1999. The statistically significant age- and sex-adjusted relative risk of 4.85 [95% confidence interval (CI) 2.72 to 8.66] between the prevalence of hallucinations on tolterodine compared with other drugs on the PEM database suggest that this is a true ADR. The significance of this relationship is again highlighted when looking at the probability of event occurrence between the cohorts, as indicated by the survival analysis. However, there is only weak evidence of a difference between terodiline and tolterodine (age- and sex-adjusted RR 1.25, 95% CI 0.62 to 2.53), with the upper 95% CI consistent with a possible doubling of risk. Hallucinations have not been reported as an adverse event for terodiline.[12] Although the anticholinergic pharmacological properties lend itself to such effects, early *in vitro* studies showed that terodiline was not associated with an effect on central catecholamine stores in animal models,[13] but this does not mean that CNS effects are not manifested through some other mechanism. This suggests that there may be some other factor inherent in populations being treated for bladder instability, contributing to the observed effect.

There is specific mention of the lack of clinical or ECG cardiac effects in premarketing studies for

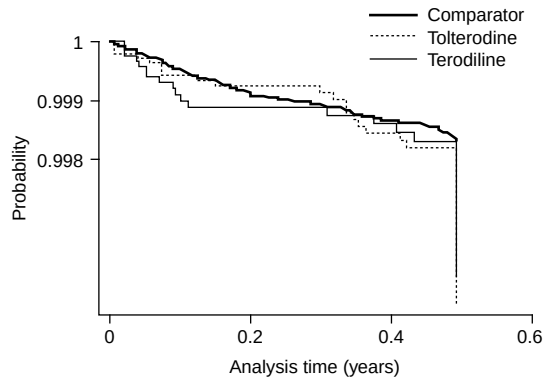

Fig. 2. Kaplan-Meier probability of remaining free from cardiac event, by drug cohort. Median time (interquartile range) [days] to event: comparator 57 (24 to 126), tolterodine 63.5 (16.5 to 135), terodiline 17.5 (6 to 62) [p = 0.4335, log-rank test].

tolterodine.[14] The MCA had received 7 reports of palpitations, 7 reports of tachycardia (2 supraventricular, 1 ventricular) and 1 report of torsade de pointes by September 9 encompassing the calendar period of this study. Although there was no significant difference for palpitation/tachycardia events in our comparison, this does not exclude the possibility of this symptom as an ADR, since we have not been able to follow up all the events of interest for the 10 comparator drugs, and thus do not know the number causally associated. Tachycardia is a known class effect of antimuscarinic drugs.[15] Palpitations are a nonspecific symptom that could be associated with many cardiac effects. In our study, there was only a weak difference in these nonserious cardiac events detected between the 2 drugs (age- and sex-adjusted RR 1.25, 95% CI 0.62 to 2.53). Patients who use tolterodine are likely to be elderly and these types of events are relatively frequent in this population.

Terodiline has been associated with arrhythmia;[10] however, in this study the number of 'probable' or 'possible' proarrythmic events associated with tolterodine was small; 4 cases (two extrasystoles and 2 atrial fibrillation), and no cases of ventricular tachycardia, torsade de pointes or sudden death. However it is likely that the study has insufficient power to discern difference at the very low incidences that could be expected for such events. Outcome misclassification is a potential bias in any study dependent on reporting by a third party: not all cardiac dysrhythmic events may have been identified, especially with lack of ECG confirmation, and there is the potential for misdiagnosis of certain events such as reflux dyspepsia which is aggravated by use of anticholinergic drugs, presenting as chest pain.

A weakness of this PEM study was that the response rate was 53.8%, and we have no guarantee that the responders were representative of all prescribers and their patients. However, we have no reason to suspect that the signals of possible ADRs were nonvalid, although the absolute rate of occurrence of events may not be valid for the whole population. We do not know whether those patients for whom a green form was not sent were likely to be different in some way from those for whom a form was sent. PEM also only relates to general practice (exposure does not include hospital prescriptions) and we have no measure of patient compliance with the dispensed drug. The strengths of this study is that it involved a large cohort of patients, of widely varying age, and who had all the concomitant illnesses and medications that are found in general practice. It thus represents actual clinical practice, free from selection bias. Furthermore, the response rate is substantial compared with the proportion of suspected ADRs that are reported in spontaneous ADR reporting schemes.[16]

Conclusion

This study provides additional evidence regarding the safety profile of tolterodine for management of detrusor instability in general practice use at the recommended dosage. Tolterodine may have been causally associated with hallucinations and tachycardia or palpitations in a few patients. Urinary incontinence is a common condition in the elderly and patients with neurological disease; anticholinergic agents should be used with caution in these high risk groups. Nevertheless, such groups may benefit from the improved tolerability, particularly in terms of incidence of anticholinergic adverse effects, that newer anticholinergic agents such as tolterodine offer.[9]

Pharmacoepidemiological studies using systematically collected data, such as PEM, identify and calculate the incidence of adverse events with increased sensitivity to rare ADRs compared with randomised controlled trials. Rarer events with an annual incidence of less than 1 : 3333, such as serious cardiac arrhythmias, will not be detected by PEM in the immediate postmarketing period in the first 10 000 patients, or will only be encountered by chance. Further epidemiological methods such as case-control studies, with further information on cases such as laboratory tests and ECGs, are required to examine the incidence of specific events among patients prescribed tolterodine in the UK.

Acknowledgements

We are very grateful to the general practitioners in England who supported this Prescription-Event Monitoring (PEM) study. We thank the Prescription Pricing Authority, the Health Authorities of England, and the Office for National Statistics, for their important participation in this study. And also we thank Dr Nick Dunn for the initial follow-up and assessment of green form reports. The Drug Safety Research Unit is a registered charity; it receives unconditional grants from pharmaceutical companies, which have no operational or editorial control on the PEM studies conducted by the Unit. The Drug Safety Research Unit has received such funds from Pharmacia & Upjohn Ltd, the manufacturers of tolterodine.

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